UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF ILLINOIS

IN RE: YASMIN AND YAZ (DROSPIRENONE) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	**3:09-md-02100-DRH-PMF**
	)	**MDL No. 2100**

This Document Relates to:

ALL CASES

CASE MANAGEMENT ORDER NUMBER 49

Regarding Motions to Exclude Testimony of Plaintiffs' Expert Witnesses
(MDL 2100 Docs. 2030, 2028, 2025, 2027)

I. INTRODUCTION

Defendants Bayer HealthCare Pharmaceuticals Inc. and Bayer Pharma AG ("Bayer") move to exclude the testimony of sixteen of the MDL plaintiffs' proffered experts. This Order resolves Bayer's motions to exclude the testimony of **Henry M. Rinder, Ph.D.** (Doc. 2027); **Charles T. Stier, Jr. Ph.D.** (Doc. 2028); **John E. Maggio Ph.D.** (Doc. 2025); and **Jan Rosing, Ph.D.** (Doc. 2030). Familiarity with the underlying proceeding is presumed. For the reasons that follow, Bayer's motions are **DENIED**.

II. BACKGROUND

This multidistrict litigation (MDL) relates to the manufacture, marketing, and sale of the prescription pharmaceuticals known as YAZ and Yasmin.[1] YAZ and Yasmin, which are manufactured, marketed, and sold by Bayer, are members of a class of prescription medicines known as combined hormonal oral contraceptives ("COCs"), which contain an estrogen and a progestin component (Doc. 2090 p. 6). The vast majority of COC's, including YAZ and Yasmin, contain the same type of estrogen – ethinyl estradiol (EE). *Id.*[2] In contrast to estrogen, the progestins in COCs are of many types. The progestin in YAZ and Yasmin is a newer type of progestin known as drospirenone ("DRSP"). *Id.*

DRSP-containing COCs are known as "fourth-generation" COCs (classified by the type of progestin used). *Id.* at pp. 6-5. COCs containing earlier developed progestins are categorized as "first-generation," "second-generation," and "third-generation." *Id.* at p. 6. First-generation COCs contain the progestin norethynodrel. *Id.* Second-generation COCs contain the progestin Levonorgestrel ("LNG") and third-generation COCs contain several progestins, including desogestrel, gestodene, and norgestimate. *Id.*

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[1] This MDL relates to other oral contraceptives that, like YAZ and Yasmin, contain drospirenone. However, YAZ and Yasmin are the subject drugs involved in the pending bellwether trials.

[2] YAZ and Yasmin differ in their dosing schedule and the amount of estrogen they contain. The Food and Drug Administration (FDA) approved YAZ and Yasmin as oral contraceptives in 2006. The FDA subsequently approved YAZ and Yasmin as a treatment for moderate acne vulgaris in women who choose to use an oral contraceptive and as a treatment for premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive.

It is generally accepted that there is an increased risk of venous thromboembolic (VTE) (blood clotting in the veins) disease in COC users (Doc. 2102-14 p. 5; Doc. 2090-2 p. 2; Doc. 2090-5 p. 5). VTE disease includes the occurrence of deep vein thrombosis (DVT) (blood clotting in a deep vein), pulmonary embolism (PE) (blood clot in the lung), and cerebral vein (sinus) thrombosis. It is also generally accepted that second-generation COCs (LNG-containing COCs) are considered to have a low risk for VTE disease (Doc. 2102-14 p. 6). Because the VTE risk associated with second-generation COCs is relatively low, LNG-containing COCs are often selected as a reference treatment in comparative studies evaluating whether there is an association between third-generation COCs and an increased risk of VTE disease (*See e.g.*, Doc. 2102-4) and in comparative studies evaluating whether there is an association between DRSP-containing COCs and an increased risk of VTE disease (*See e.g.*, Doc. 2102-14 pp. 5-6). In the mid-1990s, various reports indicated that users of third-generation COCs were at higher risk of VTE disease than users of second-generation COCs (Doc. 2090-2 p. 2).

At issue in this litigation, is the safety of DRSP-containing COCs and whether DRSP use is associated with a higher risk of VTE disease. Specifically, Plaintiffs contend that Bayer misrepresented or omitted facts pertaining to the safety and efficacy of YAZ and Yasmin. With regard to the safety of YAZ and Yasmin, plaintiffs contend that the DRSP component of the drugs is associated with an increased risk of VTE disease and of potentially life threating thrombosis

complications, including deep vein thrombosis (DVT) (a blood clot formation in one of the body's deep veins) and pulmonary embolism (a clot formation that travels to the lungs). The proffered experts addressed in this order intend to offer a range of opinions, including testimony regarding the mechanisms involved coagulation, anticoagulation, and VTE disease; the pharmacology of COCs and, in particular, the pharmacology of YAZ and Yasmin; the alleged relationship between DRSP-containing COCs' and VTE disease; and the relevant studies, data, and literature relating to COCs, coagulation, VTE disease, and/or YAZ and Yasmin.

Bayer contends that the putative experts' opinions fail to meet the requirements for admissible expert testimony under FEDERAL RULE OF EVIDENCE 702 and *Daubert v. Merrell Dow Pharms., Inc.,* 509 U.S. 579 (1993) (*Daubert*). Specifically, Bayer seeks to preclude all testimony by these individuals contending that the proffered opinions are beyond the scope of these witnesses' expertise, unreliable, irrelevant, prejudicial, and/or exceed the scope of permissible expert testimony.

III. LEGAL STANDARD

FEDERAL RULE OF EVIDENCE 702, and *Daubert v. Merrell Dow Pharms., Inc.,* 509 U.S. 579 (1993), govern the admissibility of expert testimony. The *Daubert* standard applies to all expert testimony, whether based on scientific competence or other specialized or technical expertise. *Smith v. Ford Motor Co.*, 215 F.3d 713, 719 (7th Cir. 2000) (citing *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S.137, 141 (1999)). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702. *Daubert* clarified Rule 702 charges the district court with the task of ensuring expert testimony is both relevant and reliable. *Daubert*, 509 U.S. at 589.

Courts in the Seventh Circuit conduct a three-step analysis under *Daubert*. *Ervin v. Johnson & Johnson, Inc.*, 492 F.3d 901, 904 (7th Cir. 2007).[3] First, the district court must determine whether the person whose testimony is offered is in fact an expert, as codified in Rule 702 through "knowledge, skill, experience, training, or education." *Id.* (citing Fed. R. Evid. 702). Notably, although "extensive academic and practical expertise" sufficiently qualify a potential witness as an expert, *Bryant v. City of Chicago,* 200 F.3d 1092, 1098 (7th Cir. 2000), "Rule 702 specifically contemplates the admission of testimony by experts whose knowledge is based on experience," *Walker v. Soo Line R.R. Co.*, 208 F.3d 581, 591 (7th Cir. 2000). *Smith*, 215 F.3d at 718 (citing *Kumho*, 526 U.S. at 156

[3] The Court notes the Seventh Circuit has also described the *Daubert* analysis as a two-step process. *See Chapman v. Maytag Corp.*, 297 F.3d 682, 686 (7th Cir. 2002). However, as *Chapman* simply combines the first two steps described in *Ervin* as a single test of reliability, whether the analysis is described as a three-step or two-step process does not substantively change the Court's analysis.

("[N]o one denies that an expert might draw a conclusion from a set of observations based on extensive and specialized experience.")).

Secondly, the district court must determine the expert's reasoning or methodology is reliable. *Ervin,* 492 F.3d at 904; *see Mihailovich v. Laatsch*, 359 F.3d 892, 918 (7th Cir. 2004) (citing *Kumho*, 526 U.S. at 147). Specifically, the testimony must have a reliable basis in the knowledge and experience of the relevant discipline, *Kumho*, 526 U.S. at 149 (internal quotations removed), consisting in more than subjective belief or unsupported speculation. *Chapman v. Maytag Corp.*, 297 F.3d 682, 687 (7th Cir. 2002); *Daubert*, 509 U.S. at 590.

Further, as to reliability, *Daubert* provided the following non-exhaustive list of relevant factors: "(1) whether the scientific theory can be or has been tested; (2) whether the theory has been subjected to peer review and publication; (3) whether the theory has been generally accepted in the scientific community." *Ervin*, 492 F.3d 901, 904 (7th Cir. 2007) (citing *Daubert*, 509 U.S. at 593-94). However, there is no requirement that courts rely on each factor, as the gatekeeping inquiry is flexible and must be "tied to the facts" of the particular case. *Kumho*, 526 U.S. at 150 (quoting *Daubert*, 509 U.S. at 591); *see also Chapman*, 297 F.3d at 687. Thus, "the role of the court is to determine whether the expert is qualified in the relevant field and to examine the methodology the expert has used in reaching his [or her] conclusions." *Smith*, 215 F.3d at 718 (citing *Kumho*, 526 U.S. at 153).

The district court possesses "great latitude in determining not only *how* to measure the reliability of the proposed expert testimony but also whether the

testimony is, in fact, reliable." *United States v. Pansier*, 576 F.3d 726, 737 (7th Cir. 2009) (citing *Jenkins v. Bartlett*, 487 F.3d 482, 489 (7th Cir. 2007)). Accordingly, the court's gatekeeping function requires focus on the expert's methodology; "[s]oundness of the factual underpinnings of the expert's analysis and the correctness of the expert's conclusions based on that analysis are factual matters to be determined by the trier of fact." *Smith*, 215 F.3d at 718 (citing *Daubert*, 509 U.S. at 595; *Walker,* 208 F.3d at 587).

Resolution of an expert's credibility or the correctness of his or her theories is left to the jury's determination after opposing counsel has cross-examined the expert at issue. *Id.* (citing *Walker*, 208 F.3d at 589-90). Thus, "[i]t is not the trial court's role to decide whether an expert's opinion is correct. The trial court is limited to determining whether expert testimony is pertinent to an issue in the case and whether the methodology underlying that testimony is sound." *Id.* (citing *Kumho*, 526 U.S. at 159 (Scalia, J., concurring) (stating that the trial court's function under *Daubert* is to exercise its discretion "to choose among reasonable means of excluding expertise that is fausse and science that is junky")). However, as an expert must explain the methodologies and principles that support his or her opinion, he or she cannot simply assert a "bottom line" or *ipse dixit* conclusion. *Metavante Corp. v. Emigrant Sav. Bank*, 619 F.3d 748, 761 (7th Cir. 2010) (quoting *Minix v. Canarecci*, 597 F.3d 824, 835 (7th Cir. 2010)).

Lastly, the district court must consider whether the proposed testimony will assist the trier of fact in its analysis of any issue relevant to the dispute. *See*

Smith, 215 F.3d at 718; *Chapman*, 297 F.3d at 687; *Daubert*, 509 U.S. at 592. It is crucial that the expert "testify to something more than what is 'obvious to the layperson' in order to be of any particular assistance to the jury.'" *Dhillon v. Crown Controls Corp.,* 269 F.3d 865, 871 (7th Cir. 2001) (quoting *Ancho v. Pentek Corp.,* 157 F.3d 512, 519 (7th Cir. 1998)). However, the expert need not have an opinion as to the ultimate issue requiring resolution to satisfy this condition. *Smith,* 215 F.3d at 718 (citing *Walker*, 208 F.3d at 587).

IV. ARGUMENT AND ANALYSIS

A. Motion to Exclude Certain Testimony of Jan Rosing, Ph.D. (Doc. 2030)

1. Dr. Rosing's Proffered Opinions

Plaintiffs intend to call Dr. Rosing at trial to testify regarding the effect of oral contraceptives on clotting factors. Dr. Rosing opines that DRSP-containing oral contraceptives cause an increase in blood-clotting risk factors over safer alternatives, including second-generation OCs (Doc. 2102 p. 14). Dr. Rosing will offer testimony regarding APC^{res} and his ETP-based APC^{res} test. Dr. Rosing opines that increased APC^{res} under the ETP-based test is associated with an increased risk of VTE disease. *Id*. at pp. 5-7. He further posits that, in 2004 when Dr. Rosing's ETP-based study was published, Bayer should have known DRSP-containing COCs posed an increased risk of VTE. *Id*. at p. 6.

Dr. Rosing intends to present the results of his prior tests of subjects who participated in Schering Study A25966, along with his analysis of subsequent coagulation studies and recently published epidemiological data, which Dr.

Rosing opines shows that women taking DRSP-containing COCs suffer from venous thrombosis at an increased rate consistent with the data obtained by Rosing and colleagues in 2004. *Id*. at p. 4. The results of which were purportedly available to Bayer at that time. *Id*. Dr. Rosing will also opine that sex hormone binding globulin (SHBG) data, aPTT-based APC^{res} test results, and epidemiological data are consistent with the opinions he has reached and with his ETP-based APC^{res} test results.

Dr. Rosing supports his opinions with (1) the 2004 ETP-based study; (2) two coagulation studies commissioned by Bayer[4] (3) studies evaluating sex hormone binding globulin (SHBG) levels in users of DRSP-containing COCs; (4) studies evaluating anti-coagulant and pro-coagulant variables in users of DRSP-containing COCs; and (5) epidemiological studies. *Id*. at pp. 10-11.

2. Bayer's Objections

Bayer contends that Dr. Rosing's opinion regarding the claimed effect of DRSP-containing COCs on venous thrombosis is merely an untested hypothesis and it therefore fails to meet the requirements for admissible expert opinion under Rule 702 and *Daubert* (Doc. 2030). Specifically, Bayer objects to any reliance or consideration of Dr. Rosing's ETP-based APC^{res} test, claiming that it has not been validated by the greater scientific community, is not used clinically, and has not reliably been reproduced by other scientists. *Id*.

[4] Schering Study A25966 (Doc. 2102-13; Doc. 2102-14) and a study funded by HealthCare Pharmaceuticals in 2011 (Doc. 2102-23 pp. 5,7, 11).

Bayer also objects to Dr. Rosing's reliance on and interpretation of additional data. Specifically, Bayer objects to Dr. Rosing offering testimony regarding the classical aPTT-based test results in Schering Study A25966. *Id*. at p. 11. Bayer disagrees with Dr. Rosing's analysis of those results and claims his conclusions are undercut by other evidence. *Id*. In addition, Bayer seems to assert that Dr. Rosing is not qualified to interpret these test results because he is not a clinician. Bayer further objects to Dr. Rosing relying, considering, or relating information concerning SHBG related data and literature. *Id*. Bayer contends that it is an unproven hypothesis and Dr. Rosing should not be permitted to use it to "bolster" his own hypothesis. *Id*. Finally, Bayer objects to Dr. Rosing's reliance on epidemiological studies and data. Bayer contends that such testimony is inadmissible because Dr. Rosing is not an epidemiologist and because "he did not even read through all of the major epidemiologic studies." *Id*. at pp. 12-14.

As a final matter, Bayer objects to Dr. Rosing offering any opinions that relate to the knowledge, intent, or state of mind of US Food and Drug Administration (FDA) Personnel. *Id*. In a related objection, Bayer contends that Dr. Rosing is not qualified to offer opinions on regulatory matters. With regard to this particular objection, plaintiffs respond stating that they do not intend to call Dr. Rosing to offer any state of mind testimony or regulatory testimony (Doc. 2102 pp. 23-24). Dr. Rosing does intend, however, to offer opinion testimony

based on his years of experience in the field, addressing the practicalities of proposed hemostasis studies. *Id*. at p. 24.

3. Background

a. Coagulation and APC^{res} testing

Blood clotting or coagulation is a vital step in hemostasis, the process that causes bleeding to stop. Coagulation begins after an injury to the blood vessel damages the vessel wall and exposes the blood to a protein known as tissue factor (TF). This exposure initiates a sequence of interactions involving various plasma proteins that ultimately lead to clot formation. The final step in the process occurs when a key enzyme in blood clot formation, thrombin, converts the fibrogen protein into fibrin, a "sticky" protein that is polymerized to form a blood clot.

Once bleeding stops, anticoagulants must be activated to stop the clotting process. Activated protein C (APC) is one of several anticoagulants involved in negating the clotting process. Because APC acts as an anticoagulant, plasma (the liquid in which the blood cells travel) that is resistant to APC may indicate an increased risk for VTE disease. A number of biological tests (or assays) have been developed for detecting whether an individual is APC-resistant. Generally, these tests assess the anticoagulant response of plasma to the addition of APC.

The original or "classical" APC-resistance assay, known as the aPTT-based test, evaluates the ability of APC to prolong the clotting response of plasma triggered via the "intrinsic coagulation pathway." The aPTT test has been

standardized and is commonly used in clinical laboratories around the world. In the 1990s, Dr. Rosing, developed an APC-resistance assay known as the ETP-based test (often referred colloquially as the Rosing test).[5] The ETP-based test is a measurement of the "extrinsic coagulation pathway" that evaluates the measurement of thrombin generation in plasma triggered with tissue factor (TF) in the presence or absence of added APC.[6]

b. Dr. Rosing's ETP-based Studies and Related Publications

In 1997, Dr. Rosing used the ETP-based test to evaluate APC^{res} in women taking second and third-generation COCs. In a published article addressing the results of this study, Dr. Rosing concluded that his results indicated third-generation COCs induce a higher resistance to APC than do second-generation COCs (Doc. 2102-4). In 2004, Dr. Rosing and four other scientists published an article in the *Journal of Thrombosis and Haemostasis* reporting the results of a study using the ETP-based test to measure APC resistance in women who took drospirenone-containing COCs and in women who took second-generation birth control pills. *Id*. *The* article reports that, under the ETP-based test, women exposed to DRSP-containing birth control pills exhibit an increase in APC^{res} to the same extent as women using third-generation birth control pills. *Id*. In addition

[5] The aPTT test and the ETP-based test differ in that the two assays rely on different coagulation triggers and end-points and probe different coagulation pathways.

[6] Initially, the ETP-based test was performed by hand. Since then, the ETP-based test has been revised and is now performed using a measuring apparatus called the thrombinscope. This revised measuring technique is called Calibrated Automated Thrombography (CAT).

to this article, Dr. Rosing, in collaboration with a variety of researchers, has published using the ETP-based assay in twelve other articles that were the subject of peer review (Doc. 2102-2 pp. 5-6 n. 7-19).

In 2002, Schering AG[7] initiated a study evaluating the impact of Yasmin compared to a second-generation COC on hemostasis in female volunteers (Doc. 2102-13; Doc. 2102-14) (Schering study A25966).[8] Dr. Rosing's ETP-based test was one of the parameters utilized for evaluating VTE risk in study participants (Doc. 2102-13). The ETP-based test was utilized as a "secondary" parameter because of its purported experimental status. *Id*. In addition, according to the study report, two separate independent laboratories were retained to perform the ETP-based test "due to the lack of validation of [the ETP] experimental assay." *Id*. at p. 5. Dr. Rosing's laboratory was one of the two laboratories retained to perform the ETP-based test. *Id*. The ETP-based test was utilized again as a secondary parameter in a study funded by Bayer HealthCare Pharmaceuticals in 2011 (Doc. 2102-23 pp. 5,7, 11). The study compared the hemostatic effects of a DRSP-containing COC to a non-DRSP-containing COC. *Id*. at p. 2.

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[7] In 2006, Schering AG was obtained by Bayer and officially renamed Bayer Schering Pharma AG. In 2011, Bayer Schering Pharma AG was officially renamed and is now known as Bayer Pharma AG.

[8] The study evaluated the volunteers for substantial changes in five primary hemostasis parameters (Doc. 2102-13 p. 6). These parameters were selected by a panel of experts as being "probably predictive for VTE risk." *Id*. The study also evaluated several "exploratory" secondary parameters that experts agree may be predictive for VTE risk. *Id*. Dr. Rosing's ETP-based test was included amongst these secondary parameters. *Id*.

4. Analysis

a. Qualifications

Dr. Rosing is an emeritus professor in biochemistry at the University of Maastricht in the Netherlands (Doc. 2102-5 p. 8). Dr. Rosing has more than thirty years of experience in biochemistry and specifically in studying and researching the biochemical aspects of blood coagulation (Doc. 2102-2 p. 1). As an undergraduate, Dr. Rosing studied chemistry at the University of Amsterdam, and graduated in 1970, with a specialty in biochemistry (Doc. 2102-2 p. 3. Dr. Rosing received his Ph.D. in 1974 from the University of Amsterdam in the Netherlands. *Id*. at p. 12. Since receiving his Ph.D., Dr. Rosing has acquired extensive teaching experience in subjects pertaining to biochemistry and has held numerous professional positions in his field. *Id*. at pp. 12-13.[9]

Dr. Rosing has received numerous awards and grants relating to researching various aspects of thrombosis, blood coagulation, and the mechanisms of anticoagulation. *Id*. at p. 14. In addition, Dr. Rosing has

[9] Between 1969 and 2001, Dr. Rosing has held the following professional positions: Research Assistant in the Laboratory of Biochemistry, University of Amsterdam; Research Assistant, Laboratory of Biochemistry, University of Amsterdam; Post-doctoral Research Fellow at the Department of Chemistry, University of California, Los Angeles; Post-doctoral Research Fellow at the Laboratory of Biochemistry, University of Amsterdam; Assistant Professor at the Department of Biochemistry, Maastricht University; Professor of Enzymology of Thrombosis and Haemostasis at the Department of Biochemistry, Maastricht University; Chairman of the Department of Biochemistry, Maastricht University of Limburg; and Professor of Biochemistry, Department of Biochemistry, Maastricht University. *Id*. at pp. 12-13. Dr. Rosing also holds two patents: (1) Anticoagulant factor Va derivatives and (2) Evaluation of substances for altering and for increasing APC response. Dr. Rosing is the (co)-author of more than 180 published scientific papers.

published more than 180 papers in peer-reviewed, scientific journals, the vast majority of which concern blood coagulation, and at least 34 of which have dealt specifically with the effects of hormones on the coagulation system (Doc. 2102-2 p. 1; Doc. 2102- 5 p. 25).

b. Qualification Based Objections

Bayer does not challenge Dr. Rosing's qualifications as a biochemist. The Court finds, considering Dr. Rosing's extensive education and experience, he is qualified to testify as to the various aspects of thrombosis, blood coagulation, and the mechanisms of anticoagulation. He is also qualified to offer an opinion regarding the effect of OCs on clotting factors. Further, he is qualified to offer the various opinions plaintiffs have identified in their response to Bayer's motion to exclude.

Bayer does challenge Dr. Rosing's qualifications with regard to his review and analysis of epidemiology data and of the classical aPTT-based test results in Schering Study A25966. Bayer argues that because Dr. Rosing is not an epidemiologist or clinician he cannot critically evaluate epidemiological studies or the results of Schering Study A25966. *Id*. at p. 12. The Court disagrees.

Dr. Rosing is not offering an opinion as to the validity of the epidemiological studies. He is merely positing that, assuming the tests are valid, the results are consistent with his test results and opinions. Certainly Dr. Rosing's extensive education and his professional experience, as well as his experience as a researcher and an author, qualify him to review and synthesize data and literature

from other scientific fields for the purpose of determining whether that data is consistent with his own findings. The same is true with regard to Dr. Rosing's analysis of aPTT-based test results in Schering Study A25966. This type of opinion testimony is permissible under Seventh Circuit law. *See Cooper v. Carl A. Nelson & Co.*, 211 F.3d 1008, 1020 (7th Cir. 2000); *Walker v. Soo Line R. Co.*, 208 F.3d 581, 588 (7th Cir. 2000). Moreover, examining other scientific data and literature allows Dr. Rosing to identify consistencies and inconsistencies between the fields. Consistency (or the lack thereof) among the various types of data available for analysis is an important factor in reviewing the totality of the evidence.

In addition, Bayer contends that Dr. Rosing's testimony pertaining to epidemiological studies is inadmissible because Dr. Rosing did not review *all* of the major epidemiologic studies and because Dr. Rosing's conclusions are allegedly illogical in light of contradictory epidemiological studies (Doc. 2030 pp. 13-14). The Court concludes that Dr. Rosing did not have to consider *all* of the available epidemiological studies to have sufficient data to support his opinion. If Dr. Rosing failed to consider an important epidemiological study that may be explored during cross examination. Finally, disagreement over logic is not a basis for exclusion, but rather, is fodder for cross examination in that it goes to the expert's credibility, not the admissibility of the expert's opinion.

Finally, Bayer objects to one of Dr. Rosing's proffered opinions regarding an FDA employee's (Dr. Shashaty) recommendation for prospective studies of

hemostatic variables. *Id*. at p. 24. Dr. Rosing is critical of this recommendation because it would require thousands of volunteers and many years of follow-up. *Id*. Dr. Rosing opines that not many institutions are willing to finance such expensive studies. *Id*. Bayer argues that Dr. Rosing is not qualified to make this statement because he is not a regulatory or FDA expert (Doc. 2030 p. 15).

The Seventh Circuit has noted that while "extensive academic and practical expertise" may be sufficient to qualify a witness as an expert, Rule 702 "specifically contemplates the admission of testimony by experts whose knowledge is based on experience." *Smith*, 215 F.3d at 718 (internal quotations and citations omitted). As described above, Dr. Rosing has more than thirty-five years of experience researching hemostatic variables. This is the type of "extensive hands-on experience over a meaningful period of time" that qualifies someone as an expert under Rule 702. *Jones v. Lincoln Elec. Co.,* 188 F.3d 709, 724 (7th Cir. 1999). Thus the evidence before the court shows that Dr. Rosing is qualified to testify, based on his experience, as to the practicality of proposed research studies.

c. Reliability

In addition to the qualifications already discussed, the following is pertinent to the reliability of all of Dr. Rosing's proffered opinions. In forming the statements currently at issue, Dr. Rosing consulted the following:

- Data and conclusions he and other scientists published in the Journal of Thrombosis and Haemostasis in 2004 and reaffirmed in subsequent publications (Doc. 2102 p. 13).

- Analysis of relevant studies published after his 2004 article in the Journal of Thrombosis and Haemostasis (Doc. 2102 p. 14).
- Analysis of studies conducted by or funded by Bayer. *Id*.
- Analysis of published peer reviewed studies relating to SHBG. *Id*.
- Analysis of recently published epidemiological studies relevant to the matters at issue in this litigation.

As a general matter, the Court finds that Dr. Rinder's opinions are based on a reliable scientific methodology and a sufficient foundation.

d. Assistance to the Trier of Fact

The Court finds all Dr. Rosing's opinions offer assistance to the trier of fact in its analysis of issues relevant to the dispute, as his testimony encompasses scientific opinions and observations not obvious to a lay-person.

e. Specific Objections

i. Reliability – Specific Objections Experimental Theory/ Validation by the Greater Scientific Community

Bayer argues that the ETP-based test is an experimental theory that has not been validated by the greater scientific community. Specifically, Bayer contends that Dr. Rosing's test is a novel theory, which Bayer has only used as a "secondary" parameter in hemostasis studies. In addition, Bayer argues that the ETP-based test is less established than the classical aPTT-based test and that Dr. Rosing has acknowledged the ETP-based test requires further research.

Since its development in 1997, the ETP-based test has been the subject of numerous scientific studies. Further, it has been the subject of published, peer-reviewed literature; has had its results verified in three clinical case control studies; has been used in an oral contraceptive study called for by the European

Medicines Agency; and has been used in laboratories other than Dr. Rosing's (Doc. 2102 p. 5). Accordingly, the Court finds that Dr. Rosing's test is not so novel as to render it inadmissible. Any perceived weaknesses in this regard may be explored during cross examination.

The other arguments asserted by Bayer merely indicate potential disagreement in the scientific community. For instance, although studies funded by Bayer have included qualifications regarding the predictive value of the ETP-based test, other studies contain no such qualifications (*See e.g.*, Doc. 2102-15; Doc. 2102-16; Doc. 2102-17).[10] Such disagreement does not speak to admissibility. Rather, it identifies potential weaknesses in Dr. Rosing's opinions that may be explored during cross examination. The same is true with regard to alleged differences between the classical aPTT-based test results and the ETP-based test results.

[10] As an example, a laboratory in Germany described all of the parameters utilized in its blood clotting study, which included the ETP-based test, as being "appropriate [parameters] for assessing the effect of COCs on hemostasis (Doc. 2102-15 p. 4). This particular study reportedly confirmed Dr. Rosing's prior conclusions regarding the effects of third-generation COCs on blood clotting. *Id*. In addition, when conducting a study comparing the effect of second-generaton and third-generation oral contraceptives on clotting factors, the European Medicines Agency ("EMEA", now "EMA") employed the ETP-based test as part of its analysis (Doc. 2102-21 p. 6). The EMA now lists the ETP-based test as a biological variable that should be investigated in the development of a new OC product (Doc. 2102-22 p. 6). In addition, unlike the Bayer-funded studies discussed above, the EMA does not classify the ETP-based test as an "experimental" or "secondary" parameter. *Id*. at pp. 6-7 (stating that there is no generally accepted parameter for VTE risk but identifying the ETP-based test and aPTT-based test as assays that may be predictive for VTE risk and should be evaluated).

Bayer also cites to alleged inconsistencies between the evidence and Dr. Rosing's opinions as grounds for exclusion. Specifically, Bayer contends that Dr. Rosing's opinions are undercut by another of plaintiffs' proffered experts, other studies, and aPTT-based test results (Doc. 2030 pp. 3-9). First, an expert's opinion need not be perfectly consistent with every piece of available evidence. Any such inconsistencies go to the weight of the evidence and not admissibility. Second, it is not the Court's role to decide whether Dr. Rosing's opinions are correct. *Smith v. Ford Motor Co.,* 215 F.3d 713, 719 (7th Cir. 2005). The Court is "limited to determining whether the methodology underlying [Dr. Rosing's] testimony is sound." *Id*. While the objections raised by Bayer identify potential weaknesses in Dr. Rosing's conclusions, they do not demonstrate that Dr. Rosing's methodology is unsound. Accordingly, these objections do not warrant exclusion. Bayer may vigorously attack any relevant aspect of Dr. Rosing's methodology or the basis of his opinions on cross-examination, as well as question him on any evidence that contradicts his opinions. Bayer's competing experts may also address any of the objections discussed above.

ii. Clinical Use

Bayer contends that Dr. Rosing's opinions are on shaky ground because the ETP-based test is not in clinical use. As a preliminary matter, the Court notes that "general acceptance" of a scientific theory or technique can have a bearing in determining admissibility of expert testimony. *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 594, 113 S. Ct. 2786, 125 L.Ed.2d 469

(1993). However, "[n]othing in the text of [Fed. R. Evid. 702] establishes 'general acceptance' as an absolute prerequisite to admissibility." In fact, the Supreme Court has held that "a rigid 'general acceptance' requirement would be at odds with the 'liberal thrust' of the Federal Rules and their 'general approach of relaxing the traditional barriers to 'opinion' testimony." Thus, the absence of clinical use does not necessarily preclude testimony relating to Dr. Rosing's ETP-based test.

While plaintiffs agree that the ETP-based test is not used by physicians in their clinical practice, they contend that Dr. Rosing's test results have been confirmed in three clinical case control studies. (Doc. 2102 p. 20 citing Doc. 2102-5 n. 6, 28, 29). Further, as discussed above, Dr. Rosing's ETP-based test results have been subjected to the peer review process. Considering these factors, the absence of clinical use does not warrant exclusion.

In addition, available evidence indicates Dr. Rosing's test is not in clinical use because it requires a high level of technical skill not readily available in clinical laboratories across the world. Unlike other APC^{res} tests, the ETP-based test is not performed using an "autoanalyzer" (Doc. 2102-5 p. 189). As described by Dr. Rosing, an autoanalyzer is a ready-to-use automated test; a machine that essentially performs the assay for the researcher.[11] *Id*. In contrast, Dr. Rosing's ETP-based test is performed by hand. Thus, instead of relying on an automated

[11] *See* Doc. 2102-5 p. 189 ("you put everything in a big apparatus that's called an autoanalyzer. You switch on the knob, you go out and you drink a coffee, an hour later you're back and there are your data").

system, a technician using the ETP-based test has to perform numerous time sensitive manual operations.[12] *Id*. Because clinical testing is often automated, laboratory technicians often lack the technical skills necessary to perform the ETP-based test. *Id*. at pp. 189-191.

Therefore, the absence of clinical use does not necessarily indicate the clinical community has rejected the ETP-based test. Under these circumstances, the absence of use in the clinical context goes to the weight of Dr. Rosing's opinions and not to admissibility. Accordingly, any objections pertaining to this issue should be addressed at trial during cross examination and via the presentation of competing experts.

iii. Ability to Reproduce Test Results

Bayer contends that the results of Schering Study A25966 demonstrate Dr. Rosing's test is unreliable and its results cannot be reproduced.[13] However, the accuracy of this contention appears to be subject to interpretation.[14] Further, plaintiffs have identified other studies that are consistent with Dr. Rosing's ETP-based test results, including at least one study explicitly verifying the reliability

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[12] This includes manual preparation of solutions and reagents (chemicals used in an experiment) and performing pipetting (the transfer of exact volumes of a liquid from one container to another in a controlled manner) by hand.

[13] Schering Study A25966 states that there were "large differences in individual values at comparable time points between the laboratories" (Doc. 2102-13). Both laboratories, however, reported an increased APC sensitivity ratio for both COCs, and slightly more for Yasmin. *Id*.

[14] One of plaintiffs' proffered experts, Dr. Rinder, opines that the test results from both laboratories performing the ETP-based test in Schering Study A25966 indicate a pro-coagulant change after use of DRSP-containing COCs. Dr. Rosing opines that the ETP-based test results in the Rosing study confirm that DRSP-containing COCs have a pro-thombotic effect (Doc. 2102-2 p. 6).

and reproducibility of the results (Doc. 2102-15). Thus, Bayer has not established that Dr. Rosing's test results are *impossible* to reproduce. At most, Bayer has identified a disagreement in the scientific community regarding Dr. Rosing's test results. Such disagreement is not a basis for exclusion.

Bayer also contends that Dr. Rosing's test results are difficult to reproduce. However, as discussed above, the fact that Dr. Rosing's APC^{res} assay requires a high level of technical skill and can therefore be difficult for untrained and/or inexperienced laboratory technicians to perform, does not establish that the test is unsound. The appropriate forum for addressing these arguments is at trial, during cross examination and through the presentation of competing experts.

iv. Interpretation of and Reliance on Additional Data

Bayer objects to Dr. Rosing's reliance on and interpretation of Schering Study A25966, SHBG related studies, and epidemiological studies (Doc. 2030 pp. 9-14). Bayer contends that this "other data" does not actually support Dr. Rosing's conclusions and/or that it is unreliable and untested. The Court finds that Bayer's objections relate to the weight of the evidence and not admissibility.

The fact that Bayer or its researchers disagree with Dr. Rosing's interpretation of various studies does not establish that his methodology is unsound. As with other objections raised by Bayer, these matters identify potential weaknesses in Dr. Rosing's opinions that may be explored during cross examination.

Similarly, Bayer's criticisms of SHBG related studies merely identify disagreement in the scientific community and do not warrant exclusion. Plaintiffs have presented sufficient evidence showing that SHBG data and its alleged associations have been tested and have been subjected to peer review and publication. There is no evidence that the methodology underlying SHBG data is unsound. While there may be disagreement in the scientific community with regard to how to interpret SHBG data and with regard to whether SHBG data is an appropriate measure for estrogenicity or is an appropriate surrogate marker for VTE risk in COC users, such disagreement does not warrant exclusion. Bayer's SHBG related objections can be addressed at trial during cross examination and via the presentation of contrary evidence and/or competing expert witnesses.

v. State of Mind Testimony

Bayer objects to Dr. Rosing offering any testimony regarding the intent, knowledge, or state of mind of FDA personnel. Plaintiffs respond, stating that Dr. Rosing intends to offer testimony specifying why he disagrees with various conclusions reached by Bayer's proffered experts and of Dr. Shashaty an FDA hematologist (Doc. 2102 pp. 23-24). But Dr. Rosing does not intend to offer testimony pertaining to the intent, knowledge, or state of mind of these individuals. *Id*.

B. Motion to Preclude the Testimony of Henry M. Rinder, Ph.D (Doc. 2027)

1. Dr. Rinder's Proffered Opinions

The primary questions plaintiffs would like Dr. Rinder to address for the jury are: (1) whether, on the whole, the available research data suggests a higher risk of VTE that would be of concern for a practicing clinician, and (2) whether Bayer is conveying the implications of the available data to physicians in the drug's prescribing information in a fair and balanced manner (Doc. 2090 pp. 7-8).

Dr. Rinder's opinions are based on his experience as a researcher, instructor and clinician. *Id*. at pp. 11-12. In addition, Dr. Rinder bases his opinions on his evaluation of (1) available scientific literature comparing DRSP-containing birth control pills, such as Yasmin and YAZ, with second-generation birth control pills; (2) six epidemiological studies that calculated the incidence of VTE in women taking drospirenone-containing oral contraceptives verses a second generation comparator; (3) five coagulation studies that measured changes in clotting factor levels; and (4) studies evaluating SHBG measurements. *Id*. at pp. 9-10.

After evaluating the literature described above, Dr. Rinder reached two overarching conclusions. The first is that "[f]or a clinician involved in the care of patients with risk for VTE, these data are compelling for an increased relative risk of VTE." *Id*. (citing Doc. 2090-5 p. 10). The second is that the current U.S. product label for Yasmin and YAZ does not, in Dr. Rinder's opinion as a

practicing physician, convey the total risk profile associated with that data to physicians. *Id*.

2. Bayer's Objections and Plaintiffs' Responses

Bayer objects to Dr. Rinder offering any opinions regarding an alleged association between SHBG and VTE risk (Doc. 2027 pp. 1-2, 3-8). Bayer contends that Dr. Rinder's conclusions pertaining to SHBG are inadmissible because (1) Dr. Rinder has no experience with SHBG and is therefore not qualified to opine that SHBG is a surrogate marker for increased VTE risk or that DRSP-containing COCs increase SHBG levels and (2) Dr. Rinder's SHBG opinions are based on an untested hypothesis. *Id*. at pp. 1-2, 3-8.

In response to this argument, plaintiffs state that they intend to offer Dr. Rinder to provide the following SHBG-related opinions:

- The total estrogenicity of Yasmin and YAZ, as reflected by SHBG measurements, is consistent with an increased risk of VTE. *Id*. at p. 10 (citing Doc. 2090-6 at p. 10 and Doc. 2090-5 pp. 5-6).

- SHBG results suggest a relative increase in estrogenicity associated with Yasmin and YAZ. These results are consistent with the conclusions Dr. Rinder has reached based on the epidemiologic and coagulation factor data (Doc. 2090 pp. 14-15).

Bayer also objects to Dr. Rinder offering opinions involving epidemiology or regulatory activity because these topics are outside Dr. Rinder's area of expertise. *Id*. at p. 2, 14-20. In this regard, Bayer specifically objects to Dr. Rinder offering testimony regarding the adequacy of Bayer's FDA-approved labeling and of a purportedly outdated FDA hematology memorandum from 2004. *Id.* at pp. 14-

17. Also included in this category of objections are Dr. Rinder's proffered opinions regarding an alleged association between DRSP-containing COCs and VTE risk, as well as Dr. Rinder's opinion as to the clinical significance of this alleged association. *Id*. at pp. 17-20.

Plaintiffs respond, stating that Dr. Rinder will proffer the following opinions and conclusions:

- Of the epidemiological studies reviewed, Dr. Rinder concludes that the four independent studies found DRSP-containing OCs posed a significantly higher VTE risk, the two sponsored studies found no increase in VTE risk, and that the data as a whole indicated a significant clinical concern (Doc. 2090 p. 9 citing Doc. 2090-5 p. 8).[15]

- The results of the five coagulation studies Dr. Rinder reviewed indicate that the DRSP-containing OCs induced a prothrombotic change beyond that associated with second-generation oral contraceptives. *Id*. at pp. 9-10 citing Doc. 2090-5 pp. 9-10.

- The study results, as perceived by Dr. Rinder, raise a concern for increased VTE risk with DRSP-containing [oral contracptives]," which Dr. Rinder believes is relevant to practicing physicians and should be shared by Bayer (Doc. 2090 p. 10 citing Doc. 2090-6 pp. 4-5).

- any VTE risk factor can tip balanced hemostasis into an overt clot, and so it is crucial that the risk profile associated with any particular drug be clear to physicians. *Id*. citing Doc. 2090-5 pp. 6, 10).

- The prescribing information provided to physicians (*i.e.*, the drug label) does not sufficiently warn physicians and instead provides only a partial and biased view of the available data. *Id*. citing Doc. 2090-5 p. 10.

- "[T]he labels cast the data from the two comparator studies," which suggest that Yasmin and Yaz present a higher VTE risk, "in such a way as

[15] Plaintiffs also state that since Dr. Rinder prepared his report and rebuttal, additional epidemiological studies have been published. Dr. Rinder intends to supplement his report and his opinion to reflect his review and consideration of the additional studies that are now available (Doc. 2090 p. 9 n. 4 citing Doc. 2090-5 p. 11).

> to make it appear as if that data … should be dismissed out of hand as being of any value," while "accepting the data that is favorable to Yaz and Yasmin." *Id*. citing Doc. 2090-7 p. 404.

Finally, Bayer objects to Dr. Rinder's other opinions involving DRSP's alleged mechanism of action. *Id*. at pp. 9-14. Specifically, Bayer contends that Dr. Rinder's opinions regarding (1) an alleged association involving DRSP, EE levels, and an increased VTE risk and (2) an alleged association between DRSP, APC^{res}, and an increased VTE risk are inadmissible because these topics fall outside Dr. Rinder's area of expertise and because the opinions are based unreliable methodology. *Id*.

Plaintiffs respond stating that Dr. Rinder should be permitted to provide the following opinion:

- The reports of Dr. John Maggio and Dr. Charles Stier demonstrate levels of EE are extremely high in some study subjects and vary from subject to subject. Dr. Rinder opines that this finding is consistent with his conclusion that Yasmin and YAZ carry a high VTE risk profile, as the scientific literature has reported that higher estrogen levels are associated with higher VTE risk (Doc. 2090 p. 19).

With regard to this objection, plaintiffs also contend that Dr. Rinder should be allowed to base his opinions on the following:

- Dr. Rinder should be permitted to take APC^{res} (whether measured by the aPTT-based test or the EPT-based test) measurements into account in forming his opinions. *Id*.

3. Background

a. Ethinylestradiol (EE) and VTE risk

A number of scientific studies and published articles have reported an association between an increased risk of VTE disease and the estrogen

component of COCs (Doc. 2090 pp. 5, 7; Doc. 2090-1 p. 3; Doc. 2090-5 p. 5; Doc. 2090-16 p. 3). Typically the subject estrogen is the synthetic estrogen known as ethinylestradiol (EE). Numerous studies and articles from the scientific community report that the VTE risk associated with COCs has a dose-dependent relationship with estrogen (Doc. 2090 p. 7; Doc. 2090-16 pp. 3, 9; Doc. 2090-5 p. 5). Accordingly, assessment of a COC's VTE risk profile often includes consideration of the type of estrogen used and of the drug's total estrogen content. The alleged association between VTE risk and estrogen in COC users, however, is not without criticism. There is an ongoing debate in the scientific community regarding the use of estrogen measurements as a surrogate marker for VTE risk in COC users (Doc. 2090-16 p. 9; Doc. 2090-1).

b. SHBG and VTE Risk

Traditionally, the increased VTE risk in COC users was only associated with estrogen (Doc. 2090-1 p. 3; Doc. 2090-2 p. 3). However, scientific literature has emerged which indicates that there is an association between VTE risk and the progestin components of COCs (Doc. 2090-3 p. 2; Doc. 2090-1 p. 3). Scientific literature exploring this issue has reported that the VTE risk in COC users is associated with the type of progestin used (Doc. 2090-1 p. 3). Further research indicates that some progestins counteract the prothombotic effect of estrogen, while some do not. For example, the results of a study published in the *Hemostasis, Thrombosis, and Vascular Biology journal* in 2004, suggest that, compared with a second-generation progestin (levonorgestrel) (LNG), a third-

generation progestin (desogestrel) is less effective in counteracting the thrombotic effects induced by the estrogen component in COCs (Doc. 2090-2 p.6).

Due to the observed differences in the risk of VTE purportedly induced by COCs containing the same dose of estrogen but different progestin compounds, some scientists, including Dr. Rinder, contend merely assessing the total estrogen content of a COC is not a sufficient method for evaluating VTE risk in COC users (Doc. 2090 p. 7; Doc. 2090-1 p. 4). Instead, scientists have suggested that studies evaluating VTE risk in COC users should consider the total estrogenicity – the effect of the estrogen minus the counteracting effect, if any, of the progestin (Doc. 2090 p. 7); Doc. 2090-1 pp. 3-5).

Some individuals in the scientific community have proposed SHBG, a carrier protein for estrogen and testosterone produced in the liver, as a measure for the total estrogenicity of COCs (Doc. 2090 pp. 7-8; Doc. 2090-1 pp. 3-5; Doc. 2090-3). In addition, scientists have proposed using plasma SHBG levels as a surrogate marker for the VTE risk in users of COCs. *Id*.

SHBG has been proposed as a measure for total estrogenicity because studies indicate that SHBG levels increase dose-dependently upon estrogen intake and decrease after administration of progestin (depending on the dose and type of progestin) (Doc. 2090 pp. 7-8; Doc. 2090-1 p. 4; Doc. 2090-3 p. 3). The basis for using plasma SHBG levels as a surrogate marker for VTE risk in users of COCs is scientific literature that suggests a relationship between a COCs known VTE risk and plasma SHBG levels (*See* Doc. 2090-1 pp. 4-6; Doc. 2090-3 p. 3).

Although there is a significant amount of scientific literature addressing the effect of estrogen and progestin on SHBG and reporting a possible association between plasma SHBG levels and VTE risk, SHBG findings are not without controversy. The scientific community continues to debate (1) whether it is appropriate to use SHBG as a measure for total estrogenicity and (2) whether SHBG plasma levels accurately predict VTE risk (*i.e.* is SHBG an appropriate surrogate marker or parameter for VTE risk).

c. APC^{res}

APC^{res} and the related tests for APC^{res} are discussed above in the Court's evaluation of the proffered testimony of Dr. Rosing.

4. Analysis

a. Qualifications

Henry M. Rinder Ph.D. is an attending physician in hematology and laboratory medicine at Yale-New Haven Hospital (Doc. 2090-5 p. 1). Dr. Rinder's clinical practice over the past 19 years has included the diagnosis and treatment of VTE disease which includes DVT, PE, and cerebral vein (sinus) thrombosis. *Id*. at p. 2. He has diagnosed and treated hundreds, if not thousands of patients with VTE. *Id*.

Dr. Rinder is also a Professor of Laboratory Medicine and Internal Medicine (Hematology) at Yale University. *Id*. at pp. 1-2. Dr. Rinder's research at Yale University has been concerned with the science of blood clotting and bleeding. *Id*. at p. 1. Aside from research and clinical practice, Dr. Rinder teaches hematology

to medical students, physician assistant students, residents, and fellows throughout the Yale-New Haven Health System and other Yale University School of medicine affiliated training programs. *Id*. at p. 2.

Dr. Rinder has written multiple textbook chapters on thrombosis and bleeding, and is one of the editors of the text "Hematology in Clinical Practice." *Id*. In the past ten years, Dr. Rinder has published two peer-reviewed articles based on his original research. *Id.* at p. 21. Dr. Rinder has also authored or co-authored more than sixty articles addressing various topics associated with his area of expertise in numerous scientific and clinical journals. *Id*. at pp. 21-26.

b. Qualification Based Objections

Bayer does not dispute that Dr. Rinder is well-qualified as a hematologist generally (Doc. 2137 p. 2). However, Bayer challenges Dr. Rinder's ability to analyze and draw conclusions from epidemiological research, since he is not an epidemiologist. Bayer also contends that Dr. Rinder cannot testify about studies involving SHBG, APC^{res}, and EE because Dr. Rinder is not an expert in these matters.

With regard to Bayer's objections to Dr. Rinder's testimony about epidemiological studies, the fact that Dr. Rinder is not an epidemiologist is not at all decisive. *See Doe v. Cutter Biological, Inc.*, 971 F.2d 375, 385 (9th Cir. 1992) ("Ordinarily, courts impose no requirement that an expert be a specialist in a given field, although there may be a requirement that he or she be of a certain profession, such as a doctor."). This is particularly evident in light of Dr. Rinder's

credentials as a researcher, instructor, and published author, as well as a clinician, and his ability to analyze the epidemiological research, as demonstrated in his report. Further, as Dr. Rinder explained during his deposition, "as part of what I always do in my evaluations of hematologic disorders and problems, I read the literature, and a lot of that literature has to do with epidemiology and statistics and populations." (Doc. 2090-7 p.116).

Considering these factors, clearly, Dr. Rinder is capable of understanding the data reported in studies conducted by epidemiologists. Further, Dr. Rinder has appropriately summarized the underlying reports. *See* Fed. R. Evid. 1006 (permitting summary evidence); *United States v. Pree*, 408 F.3d 855, 869-870 (7th Cir. 2005) (approving use of an "expert summary witness" who is permitted both to summarize evidence for the jury and to offer an expert analysis of the facts). Accordingly, Dr. Rinder may testify about his review of the epidemiological studies and his conclusions based thereon. "[A]ny questions or problems concerning the expert's testimony may be thoroughly explored during cross-examination of the witness." *United States v. Gonzalez*, 933 F.2d 417, 429 (7th Cir. 1991).

Bayer's objections concerning whether Dr. Rinder is qualified to analyze and draw conclusions from scientific literature relating to EE, SHBG, and APC^{res} (in particular Dr. Rosing's ETP-based test) mirror its arguments concerning his ability to evaluate and opine as to epidemiology data. Thus, the Court similarly finds Dr. Rinder's years of experience as a clinician, researcher, instructor, and

publish qualify him to opine generally as to the relative safety of Yasmin and YAZ based on his interpretation of the relevant literature.

Finally, Bayer contends that Dr. Rinder is not qualified to offer testimony with regard to FDA regulatory matters. Plaintiffs respond, stating that Dr. Rinder does not intend to offer testimony with regard to whether Bayer complied with FDA regulatory requirements when it issued its label (Doc. 2090 p. 21). Rather, Dr. Rinder intends to opine, based on his extensive background and on his review of the relevant literature, regarding the VTE risk associated with YAZ and Yasmin. Dr. Rinder also intends to opine, based on his experience as a practicing physician, as to whether the relevant warning labels accurately and fairly convey that risk. Dr. Rinder is fully qualified to offer an opinion as to the risks and benefits of drugs and to compare that knowledge with what was provided on the label – such testimony does not require any regulatory expertise. Dr. Rinder may also offer an opinion explaining why he disagrees with the conclusions drawn in the 2004 FDA memorandum. The Court finds Bayer's objections to this testimony to be unconvincing.

c. Reliability

In addition to the qualifications already discussed, Dr. Rinder reviewed a variety of relevant scientific literature and data. Dr. Rinder's list of literature references contains 23 articles, including scientific literature comparing DRSP-containing birth control pills, such as Yasmin and YAZ, with second-generation birth control pills; (2) epidemiological studies that calculated the incidence of VTE

in women taking drospirenone-containing oral contraceptives verses a second generation comparator (3) coagulation studies that measured changes in clotting factor levels; and (4) studies evaluating SHBG measurements (Doc. 2090 pp. 9-10; Doc. 2090-5 pp. 13-16).

As a general matter, the Court finds that Dr. Rinder's opinions are based on a reliable scientific methodology and a sufficient foundation.

d. Assistance to the Trier of Fact

The Court finds all of Dr. Rinder's opinions offer assistance to the trier of fact in its analysis of issues relevant to the dispute, as his testimony encompasses scientific opinions and observations not obvious to a lay-person.

e. Specific Objections

i. Opinions Relating to Other Experts and Publications

Bayer contends that Dr. Rinder's opinions are improperly grounded on the opinions of others and on studies that Dr. Rinder did not personally participate in. The Court finds that, in the instant case, such reliance is not inappropriate and does not warrant exclusion. "[A]n expert is permitted wide latitude to offer opinions, including those that are not based on first-hand knowledge or observation." *See Daubert*, 509 U.S. at 592. *See also Walker v. Soo Line R. Co.*, 208 F.3d 581, 588 (7th Cir. 2000) ("[C]ourts frequently have pointed to an expert's reliance on the reports of others as an indication that their testimony is reliable."). That Dr. Rinder considers information from others in forming his own conclusions does not necessitate the exclusion of his testimony. "[I]t is common in

technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert knowledge not possessed by the first expert; and it is apparent from the wording of Rule 703 that there is no general requirement that the other expert testify as well." *Dura Automotive Systems of Indiana, Inc. v. CTS Corporation*, 285 F.3d 609, 613 (7th Cir. 2002).[16] Such testimony need only be excluded when an expert is "just parroting the opinion" of another expert. *Id*. Otherwise, an expert may rely on information provided by non-testifying experts, so long as he does not merely serve as a spokesman for the absent expert, vouching for the truth of his statements. *In re James Wilson Associates*, 965 F.2d 160, 172-73 (7th Cir.1992).

Moreover, Rule 702 states that an expert's testimony must be "based on sufficient facts or data." Dr. Rinder based his testimony on information he obtained from other experts on the issue of increased risk of VTEs posed by Yaz and Yasmin. That is permissible. The Advisory Notes to the 2000 Amendments to Rule 702 make clear that "[t]he term 'data' is intended to encompass the reliable opinions of other experts." Relying on the published works of other professionals is permissible in medicine, as it is in other fields. 33A FED. PROC., L.ED. § 80:251 (2008).

[16] The Supreme Court has written that "a judge assessing a proffer of expert scientific testimony under Rule 702 should also be mindful of other applicable rules." *Daubert*, 509 U.S. at 595. The Court explicitly suggested that lower courts consider Federal Rule of Evidence 703, which permits experts to use facts or data "of a type reasonably relied upon by experts in the particular field." *Id*.

A review of Dr. Rinder's report makes it clear that Dr. Rinder is not merely parroting the views of others. Dr. Rinder conducted independent analysis of the available literature to arrive at his conclusions regarding an increased relative risk of VTE for patients using DRSP-containing COCs. He also independently reviewed the opinions of two of plaintiffs' pharmacology experts, concluding that the reported levels of EE were consistent with his conclusion that Yasmin and YAZ carry a high VTE risk profile. Similarly, he considered APC^{res} literature and SHBG literature to corroborate his own conclusions about the VTE risk profile of YAZ and Yasmin. As Dr. Rinder has conducted a fully independent analysis of the matter, the court concludes Dr. Rinder is entitled to offer opinions resulting from that analysis.

ii. Science that is Allegedly Novel or Experimental

Plaintiffs have identified at least four published studies evaluating the relationship between VTE risk in COC users and SHBG levels (Doc. 2087 pp. 17-18).[17] There is nothing novel, experimental, or unsound about the methodology used in these studies. For example, one of the cited studies, utilizing data available in the literature, evaluated the relationship between the reported risk of VTE with various COC brands with the reported effects on SHBG of the same brands (*See e.g.*, Doc. 2090-1 p. 4). There is nothing novel, experimental, or unsound about this methodology. After reviewing the data, the researchers

[17] Plaintiffs also note that Bayer has looked at or examined SHBG in a total of 12 clinical studies evaluating DRSP/EE compounds (Doc. 2090 p. 10 n.6).

conducting this study concluded that there "appears to be a relationship between the risk of VTE and the effect of the same COC on SHBG" (Doc. 2090-1 p. 5). Because there is nothing novel, experimental, or unsound about the methodology this study (or other similar studies cited by the plaintiffs) used in reaching this conclusion there is no ground for excluding the testimony regarding the alleged association.

This, however, is not the end of the story. The central dispute with regard to SHBG studies is whether SHBG is an appropriate measure of estrogenicity and whether it may serve as a surrogate marker for VTE risk. Some researchers have concluded that using SHBG in this manner is appropriate (*See e.g.*, Doc. 2090-1). Bayer and its researchers, however, disagree. Bayer and its researchers contest the validity of SHBG as a measure of estrogenicity and as a surrogate marker for VTE risk. Nonetheless, Bayer often utilizes SHBG measurements in clinical studies evaluating the risk profile of various COCs. Bayer does limit its use of SHBG measurements in these trials, generally noting that it is merely a "secondary" or "exploratory" parameter and/or stating that SHBG is not a proven predictor of VTE risk.

All things considered, Bayer's SHBG objections, merely demonstrate a disagreement amongst scientists with regard to how to interpret the results of studies reporting an association between SHBG levels and VTE risk. This difference of opinion is not grounds for exclusion. Differing expert opinions as to the significance or interpretation of scientific evidence is one of the principal

purposes of expert cross examination. It is up to the jury to decide which interpretation is most credible. Accordingly, Dr. Rinder may testify as to studies and publications involving SHBG and VTE risk. He may also opine as to whether these studies or publications are consistent with the opinions he has formed with regard YAZ, Yasmin, and VTE risk. Bayer can address any perceived weaknesses in Dr. Rinder's opinions via cross examination and through the presentation of contrary evidence or competing experts.

Bayer's objections regarding exclusion of testimony relating to EE literature or studies mirror its arguments concerning Dr. Rinder's proffered SHBG testimony. Plaintiffs have identified numerous published studies reporting a dose dependent relationship between oral intake of EE and VTE risk (Doc. 2090-1 p. 3). Similarly, there is a significant amount of literature identifying a dose dependent relationship between oral intake of EE and SHBG levels (Doc. 2090-1 p. 4 ref. 15-24).[18] There is no indication that the studies reporting these associations employed unsound methodology. Accordingly, Dr. Rinder is free to

[18] In a recent study evaluating the safety profile of another Bayer oral contraceptive, researchers examined estrogen levels, stating "[i]t is generally well accepted that the influence of COCs on coagulation and fibrinolysis depends mainly on the estrogen component of the regimen (Doc. 2090-16 p. 9). Notably, when evaluating the potency of the progestin used in the study, the researchers relied on clinical studies assessing SHBG (among other things) (Doc. 2090-16 p. 9). This study also stated "the adverse effects on hemostatic variables are most likely to be influenced by the estrogen type and dose. Although hemostatic surrogate parameters are not predictive of the occurrence of thromboembolic events, their evaluation is part of the development process of COCs." (Doc. 2090-16 p. 3).

testify regarding the results of studies evaluating the relationship, if any, between EE and SHBG levels and/or VTE risk.

Dr. Rinder is also permitted to form an opinion based on opinions offered by Dr. Maggio and Dr. Stier. He may opine with regard to whether their conclusions are consistent with his conclusion that Yasmin and YAZ carry a high VTE risk profile.

The Court is also not persuaded by Bayer's objections to any testimony involving APC^{res} and, in particular, APC^{res} as measured by Dr. Rosing's ETP-based assay. Plaintiffs have identified numerous published studies indicating that APC^{res} is a valid marker for VTE risk in COC users. Indeed, even Bayer has stated that APC^{res} (as reported using the classical aPTT-based test) is primary marker which most experts would accept as being "probably predictive" of VTE risk (Doc. 2102-13 p. 6).

As discussed previously, there is disagreement over various aspects of Dr. Rosing's ETP-based APC^{res} test. Although the ETP-based test is a relatively new assay, it appears to be gaining acceptance as a method for evaluating the risk profile of COCs.[19] Moreover, Dr. Rosing's results have been confirmed and evaluated in numerous published peer-reviewed articles. Accordingly, the ETP-based test is not so novel as to warrant exclusion. Bayer's objections in this

[19] In Schering Study A25966 researchers note that "the scientific discussion on validity and predictive value of hemostasis laboratory parameters is moving fast." (Doc. 2102-14 p. 5).

regard can be explored at trial during cross examination and via the presentation of contrary evidence and/or competing expert witnesses.

In sum, the Court finds that Dr. Rinder may consider APC^{res} (as measured by the aPTT-based test or the ETP-based test) in forming his opinions and may present testimony regarding the same.

C. Motion to Exclude Certain Testimony of Charles T. Stier, Jr., Ph.D. (Doc. 2028)

1. Dr. Stier's Opinions – Generally

Plaintiffs seek to present opinion testimony by Dr. Stier, based on his expertise, research, and his review of epidemiologic and scientific literature, that fourth-generation COCs containing DRSP, such as Yasmin and YAZ, produce a risk of VTE that is at least as high or greater than the VTE risk of third-generation COCs and double the VTE risk of second-generation COCs containing LNG.

Dr. Stier examines both the pharmacodynamics and pharmacokinetic interactions associated with ingestion of both Yasmin and YAZ, as well as the intrinsic effects of such ingestion (Doc. 2087 p. 8; Doc. 2087-1 p. 3). Regarding pharmacodynamics, Dr. Stier opines that certain studies show that DRSP-containing COCs produce marked increases in plasma concentrations of SHBG much greater than those seen in second and even third generation COCs (Doc. 2081 p. 8; Doc. 2087 pp. 4,5). Dr. Stier contends that SHBG is used to indicate the balance of estrogenic and androgenic activities and thus reflects net estrogenicity (Doc. 2081 p. 8; Doc. 2087 p. 5). Dr. Stier also reports that SHBG level has been found to positively correlate with VTE risk.

Dr. Stier attributes the increased SHBG levels produced by COCs containing DRSP to the antiandrogenic properties of DRSP (Doc. 2081 p. 8; Doc. 2087 p. 5). He also contends that SHBG binds to testosterone with high affinity and thus increases in SHBG can decrease free testosterone levels (Doc. 2081 p. 8; Doc. 2087 pp. 4-5). Dr. Stier further opines that the pharmacodynamic attributes of DRSP are familiar to pharmacology and are seen in another fourth generation progestin, CPA (Doc. 2081 p. 8; Doc. 2087 p. 5).

Dr. Stier also offers opinion testimony regarding pharmacokinetic interactions, concluding that DRSP increases the magnitude and duration of estrogen's interaction with its receptors, which may increase the patient's estrogenic exposure regardless of the EE dose contained in the COC (Doc. 2081 p. 9; Doc. 2087 pp. 3,5). Dr. Stier also offers testimony regarding enterohepatic recirculation and the drugs' half-life (Doc. 2081 p. 9).

Dr. Stier offers opinions based on Bayer clinical study reports regarding EE levels in COC users. *Id*. In addition, Dr. Stier opines that the intrinsic properties of DRSP promote thrombosis independent of its interaction with EE. *Id*. Finally, Dr. Stier asserts that his opinions are consistent with other hematological and epidemiological literature. *Id*. at p. 10.

2. Bayer's Objections and Plaintiffs' Responses

Bayer objects to Dr. Stier advancing any opinions related to a study[20] of pig uteruses that did not involve DRSP (Cardenas study) and to two studies by Oelkers[21] regarding DRSPs alleged toxic effects on blood vessels (Oelkers studies) (Doc. 2028 pp. 1-7).

Plaintiffs respond to this argument stating that Dr. Stier intends to offer the following testimony:

- Dr. Stier intends to summarize the animal research study for general background purposes only (Doc. 2087 p. 6). The animal research study is not the basis for any opinion of "theory" articulated by Dr. Stier. *Id*.

- Dr. Stier intends to cite to the Oelkers study only for the proposition that DRSP is associated with increased release of the enzyme renin. Dr. Stier does not base opinions comparing the effects of DRSP on the vasculature to cigarette smoking or advancing age on the Oelkers studies. *Id*. at p. 7.

Bayer also contends that Dr. Stier proffers an array of opinions on the YAZ and Yasmin labels and on clinical practice (Doc. 2028 p. 2). Bayer objects to these opinions because Dr. Stier lacks expertise in drug labeling and is not a medical doctor, does not treat patients or prescribe medicine. *Id*.

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[20] *See* H. Cardenas, *et al*., Attenuation of Estrogenic Effects by Dihydrotestosterone in the Pig Uterus is Associated with Downregulation of the Estrogen Receptors, Biology of Reproduction (2003) (Doc. 2028-3)

[21] *See* W. Oelkers, *et al*., Dihydrospirorenone, a New Progestin with Antimineralocorticoid Activity: Effects on Ovulation, Electrolyte Excretion, and the ReninAldosterone System in Normal Women, J. Clinical Endocrinology & Metabolism (1991) (Doc. 2028-4); W. Oelkers, *et al.*, Effects of a New Oral Contraceptive Containng an Antimineralocortoid Progestin, Drospirenone, on the Renin_Aldosterone System, Body Weight, Blood Pressure, Glucose Tolerance, and Lipid Metabolism, J. Clinical Endocrinology & Metabolism (1995) (Doc. 2028-5).

Plaintiff responds to this argument stating that Dt. Stier intends to proffer the following testimony:

- Dr. Stier is not being offered to opine on regulatory or clinical matters (Doc. 2087 p. 7).

- Dr. Stier does intend to discuss the factual contend of the Yasmin and YAZ labels and to relate facts regarding the actual use of these drugs. *Id*. Specifically, Dr. Stier will testify to the following:

    - Discrepancies between the EE delivery and variability levels listed in the labels for Yasmin and YAZ and data reported studies. *Id*. at p. 21.

    - SHBG levels are reported in labeling and product inserts for other oral contraceptives. *Id*.

Bayer contends that Dr. Stier is not qualified to consider studies that address APC^{res} and SHBG in relation to DRSP and VTE risk because Dr. Stier is not a specialist in hematology (Doc. 2028 pp. 7-8). Specifically, Bayer contends that Dr. Stier is not qualified to testify about SHBG because he lacks knowledge the underlying SHBG biological processes. In addition, Bayer objects to reliance on any such studies because they are purportedly based on unsettled science. *Id*. For these reasons, Bayer seeks to exclude any testimony pertaining to APC^{res} and SHBG.

Plaintiffs respond stating that Dr. Stier intends to offer the following testimony on these matters:

- There is a correlation of SHBG levels associated with Bayer's products and VTE risk (Doc. 2087 p. 16).

Bayer contends that Dr. Stier's proffered testimony regarding the levels of exposure of EE for women taking Bayer's products and the variability of such EE

exposure levels lacks a sufficient basis and should be excluded (Doc. 2028 pp. 9-10).

Plaintiffs respond stating that Dr. Stier intends to offer the following testimony on these matters:

- Dr. Stier opines that DRSP-containing COCs expose patients to greater and more variable levels of EE than other COCs (Doc. 2087 p. 20).
- Dr. Stier's opinions on this matter are based on Bayer's clinical studies and reports. *Id*.

3. Analysis

a. Qualifications

Dr. Stier is an assistant professor of pharmacology and researcher at New York Medical College (Doc. 2087 p. 6). Dr. Stier received a Ph.D. in pharmacology from Columbia University in 1978 (Doc. 2087-1). He is an associate professor in the Department of Pharmacology of New York Medical College, a position he has held since 1990. He is a current member of the American Society of Nephrology, the American Heart Association and the American Society of Pharmacology and Experimental Therapeutics, among other professional organizations. *Id*. He currently serves on the editorial boards of Cardiovascular Drug Reviews and Current Hypertension Reviews and is co-executive editor of the American Journal of Hypertension. *Id*. In his capacities as an instructor and advisor to medical and graduate students, editor and pharmacological researcher, Dr. Stier routinely reviews a wide range of data and analyses from other scientific and technical disciplines (Doc. 2087-2 pp. 67, 78,

79, 82-84, 88). Finally, from 2000 to 2004 Bayer HealthCare Pharmaceuticals Inc. engaged Dr. Stier as a pharmacological consultant to examine DRSP and spironolactone, another drug that is chemically related to DRSP (Doc. 2087 p. 11).

Given Dr. Stier's education, as well as his professional, academic, and research experience. The Court concludes that Dr. Stier is qualified to testify as to the opinions discussed above.

b. Qualification Based Objections

Bayer does not challenge Dr. Stier's qualifications as a pharmacologist. However, Bayer contends that Dr. Stier, as a pharmacologist (and not a hematologist, clinician, or regulatory expert), is not qualified to offer opinions on SHBG, APC^{res}, epidemiology, labeling, and clinical practice.

With regard to opinions on labeling and clinical practice, plaintiffs have stated that Dr. Stier will not present any testimony regarding FDA labeling or clinical requirements (Doc. 2087 p. 21). Plaintiffs state that Dr. Stier does intend to offer factual observations about the content of Bayer's labels. *Id*. Specifically, Dr. Stier intends to discuss discrepancies between the EE delivery and variability levels listed in the labels for Yasmin and YAZ and data reported in studies. *Id*. Dr. Stier also intends to relate that SHBG levels are reported in labeling and product inserts for other oral contraceptives. *Id*. The Court agrees that the testimony described by plaintiffs is factual testimony and not subject to exclusion under Rule 702.

As to the four purportedly improper clinical opinions cited by Bayer, the Court agrees with plaintiffs. The referenced statements are factual assertions regarding the actual use and prescription of certain drugs. Accordingly, these statements do not warrant exclusion under Rule 702.

The Court next considers Bayer's objections regarding whether Dr. Stier is qualified to address issues relating to SHBG and APC^{res} because he is not a hematologist. First, the fact that Dr. Stier is not a hematologist is not at all decisive. *See Doe v. Cutter Biological, Inc.*, 971 F.2d 375, 385 (9th Cir. 1992) ("Ordinarily, courts impose no requirement that an expert be a specialist in a given field, although there may be a requirement that he or she be of a certain profession, such as a doctor."). This is particularly evident in light of Dr. Stier's credentials as an instructor, author and editor, and researcher – particularly his experience in pharmacological research. Further, Dr. Stier testified that he has extensive experience in reviewing a wide range of data and analyses from other scientific and technical disciplines. Considering the above, the Court finds that Dr. Stier is clearly capable of understanding the data reported in studies evaluating SHBG and APC^{res}. He may offer testimony on these matters, including testimony regarding whether the available data is consistent with his conclusions.

Bayer also contends that Dr. Stier is unqualified to testify regarding SHBG and APC^{res} because he lacks knowledge as to the underlying biological processes. Rule 702, however, does not require such knowledge. Dr. Stier's background and

experience sufficiently establish that he is qualified to analyze scientific literature addressing both SHBG and APC^{res}.

c. Reliability

In addition to the qualifications already discussed, the following is pertinent to the reliability of all of Dr. Stier's proffered opinions. In forming the statements currently at issue, Dr. Stier consulted the following:

- Studies, including Bayer studies, evaluating DRSP-containing COCs (Doc. 2087 p. 8).
- Relevant hematological literature and data, including literature addressing SHBG, APC^{res}, and EE in relation to coagulation, COC use, and/or VTE risk. *Id*. at pp. 10, 12-13.
- Relevant epidemiologic studies and data. *Id*. at p. 12.
- Relevant pharmacology literature. *Id*. at p. 13.

As a general matter, the Court finds that Dr. Stier's opinions are based on a reliable scientific methodology and a sufficient foundation.

d. Assistance to the Trier of Fact

The Court finds all Dr. Stier's opinions offer assistance to the trier of fact in its analysis of issues relevant to the dispute, as his testimony encompasses scientific opinions and observations not obvious to a lay-person.

e. Specific Objections

i. Objections Pertaining to the Cardenas Study

Bayer contends that Dr. Stier's reasoning is unreliable because it is based on the Cardenas study (Doc. 2028 pp. 2-4). The Cardenas study did not involve drospirenone. It showed that dihydrotestosterone, an androgen, regulates pig estrogen receptors. *Id*. Plaintiffs contend that Dr. Stier did not rely on the

Cardenas study for his opinion regarding an increased risk of thrombosis associated with DRSP-containing COCs (Doc. 2087 p. 14). Plaintiffs state that Dr. Stier merely cites to the study as an example of a pharmacodynamics interaction – specifically, the down-regulation of estrogen receptors in pig uteruses caused by dihydrotestosterone. Because no opinion testimony is in issue, the Court concludes that Rule 702 and the case authority cited by Bayer do not apply. Dr. Stier may relate facts pertaining to the Cardenas study for the limited purpose of providing an example of a pharmacodynamics interaction.

ii. Objections Pertaining to the Oelkers Studies

Bayer contends that Dr. Stier posits that two studies by Oelkers, which suggested that women may reap health benefits from DRSP-containing medicines, actually demonstrate that YAZ and Yasmin pose risks akin to cigarette smoking and aging (Doc. 2028 p. 4). Plaintiffs contend that Dr. Stier does not cite to the Oelkers studies for that proposition (Doc. 2087 p. 15). Instead, he is only citing to the Oelkers studies as support for the proposition that DRSP is associated with increased renin release. *Id*. The report of the 1995 Oelkers study directly supports this proposition (Doc. 2028-5 p. 1818). Because Dr. Stier only cites to the Oelkers studies as support for this limited proposition, the Court need not address the argument that this particular opinion cannot be derived from the referenced studies. Dr. Stier may reference the Oelkers studies for the limited purpose of addressing DRSP's purported association with increased renin release.

iii. SHBG and VTE Risk

Dr. Stier opines that DRSP's alleged effect on SHBG can be used to suggest that YAZ and Yasmin increase the risk of VTE. He further opines that there is a "well-known association between increased SHBG levels and increased APC^{res}, which is considered by some researchers to be predictive of VTE risk." (Doc. 2087-1 p. 8). Aside from arguing that Dr. Stier is not qualified to offer such an opinion, Bayer argues that there is no foundation for such an opinion. The Court disagrees.

As previously noted, plaintiffs have identified at least four published studies evaluating the relationship between VTE risk in COC users and SHBG levels (Doc. 2087 pp. 17-18).[22] There is nothing novel, experimental, or unsound about the methodology used in these studies. A number of researchers in published peer-reviewed articles have concluded that there seems to be a relationship between the risk of VTE and a COC's effect on the patient's SHBG levels (*See e.g.*, Doc. 2090-1 p. 5). Accordingly, there is sufficient foundation for Dr. Stier's SHBG related opinions.

The Court notes that there is dispute with regard to whether SHBG is an appropriate measure of estrogenicity and whether it may serve as a surrogate marker for VTE risk. However, for reasons already discussed, the Court finds that this disagreement does not warrant exclusion of SHBG related testimony.

[22] Plaintiffs also note that Bayer has looked at or examined SHBG in a total of 12 clinical studies evaluating DRSP/EE compounds (Doc. 2090 p. 10 n.6).

Accordingly, Dr. Stier may testify as to studies and publications involving SHBG and VTE risk. He may also opine as to whether these studies or publications are consistent with the opinions he has formed with regard YAZ, Yasmin, and VTE risk. Bayer can address any perceived weaknesses in Dr. Rinder's opinions via cross examination and through the presentation of contrary evidence or competing experts.

iv. EE Exposure and Variability

Dr. Stier also contends that DRSP-containing COCs expose women to greater and more variable amounts of EE than other COCs, thereby increasing the risk of VTEs. Plaintiffs contend that Dr. Stier's testimony regarding EE exposure and variability for Yasmin and YAZ is based on reports of Bayer's own clinical studies (Doc. 2087 p. 20). Considering Dr. Stier's background and professional expertise, he is certainly qualified to review clinical study reports and draw conclusions based on those results. To the extent that Bayer disagrees with Dr. Stier's conclusions they can rigorously attack his opinions during cross examination. Dr. Stier's failure to review other data or literature merely identifies a potential weakness in his testimony but it is not grounds for exclusion. This issue may also be explored during cross examination and through the presentation of contrary studies and/or competing expert witnesses.

D. Motion to Exclude Certain Testimony of John E. Maggio, Ph.D.,

1. Dr. Maggio's Opinions – Generally

Dr. Maggio offers expert testimony about the biological processes relevant to OCs and VTEs. Dr. Maggio provides opinions with respect to both pharmacology (the study of drug action) and pharmacodynamics (the effects the drug has on the body) (Doc. 2096 p. 1).

Dr. Maggio's opinions bear on two central issues in the case—namely, whether Bayer's product labels adequately warned consumers and physicians of the risks of Yasmin or Yaz, and; whether the pharmacologic data supports the epidemiology conclusions of an increased risk of thrombotic events as compared to that of COCs containing second-generation progestins. Based on the opinions described above, Dr. Maggio concludes:

- The variability of EE concentration for Yasmin/Yaz is much higher than for comparable OCs, and can cause a substantial number of the women to be exposed to EE levels that equal or exceed those that FDA found unacceptable, when it banned COCs >50 mcg/day of EE dueto the increased risk of VTE.

- The effects of Yasmin/Yaz on SHBG and APC resistance are consistent with those of other third or fourth generation progestins that have similarly been found to increase the risk of VTE. These important pharmacodynamic properties of Yasmin/Yaz are similar to those of COCs containing other progestins that are also associated with an increased risk of VTE in the published epidemiology studies.

- The epidemiological studies showing that Yasmin/Yaz increase the risk of VTE in comparison to COCs containing older progestins (*Id.* ¶83-104; 213) are consistent with the pharmacologic evidence.

- The totality of the evidence establishes that Yasmin/Yaz increase the risk of VTE approximately two-fold.

- Bayer's product labels are inadequate and inaccurate in their discussion of EE PK and product risks. The exposure of women to EE from Yasmin/Yaz is considerably higher than indicated on the product labels.

(Doc. 2096 pp. 11-12).

2. Bayer's Objections and Plaintiffs' Responses

Bayer seeks to exclude Dr. Maggio's testimony in its entirety. Bayer contends that Dr. Maggio's opinions are not supported by any data and are based on novel theories that are not grounded in reliable scientific method (Doc. 2025 p. 2).

The bulk of Bayer's objections address Dr. Maggio's EE related opinions. Generally, Bayer objects to Dr. Maggio's opinions regarding the amount and variability of delivery of EE in YAZ and Yasmin, contending that they are made-for-litigation and not supported by scientific authority or data (Doc. 2025 p. 2). Specifically, Bayer contends that Dr. Maggio should be precluded from (1) testifying that Yasmin and YAZ expose women to higher levels of EE than other similar dose COCs; (2) testifying that Yasmin and YAZ expose women to more EE than COCs containing 50 micrograms of EE; and (3) speculating about why Yasmin and YAZ may expose women to more EE than other COCs (Doc. 2025 pp. 3-10).

In response to Bayer's objections, plaintiffs state that Dr. Maggio will offer the following EE related opinions:

- Yasmin/Yaz produce dangerously high EE serum concentrations and EE exposures in many women, largely due to an atypically large variability (Doc. 2096 pp. 10-14).

- YAZ/Yasmin expose women to higher levels of EE than other similar dose COCs with less variability. *Id*.
- YAZ/Yasmin expose some women to levels of EE above the threshold considered safe by the FDA. *Id*.
- Bayer's PK studies are flawed and inconsistent. *Id*.

With regard to the objections to Dr. Maggio's alleged speculation, plaintiffs contend that Dr. Maggio is not speculating and intends to opine regarding alleged deficiencies and improper assumptions in pharmacology studies conducted by Bayer on DRSP, Yasmin, and YAZ. *Id*. at p. 17. It is Dr. Maggio's opinion that the alleged deficiencies and improper assumptions may result in increased exposure to the active ingredients of Yasmin/YAZ, and thereby an increasing risk of adverse effects. *Id*. at p. 18.

Bayer also objects to Dr. Maggio offering any testimony relating to APC^{res} and SHBG, claiming that Dr. Maggio, a pharmacologist, may not cite or rely on hematology research. Plaintiffs respond stating that Dr. Maggio intends to offer testimony identifying consistency between the properties of DRSP and other progestins identified as increasing the risk of VTE (Doc. 2096 p. 19).

In addition, Dr. Maggio intends to offer opinions based on his review of the relevant literature and data, as well as his conclusions based on the totality of the evidence. Dr. Maggio will not and does not opine that SHBG is a surrogate marker for VTE risk. Instead, plaintiffs contend, he points out the strengths and consistency of the data establishing a relationship between hormonal

contraceptives that increase the risk of VTE, and those that demonstrate increases in SHBG and activated Protein C resistance.

Bayer also contends that Dr. Maggio offers opinions in a number of other areas where he is not qualified, including testimony regarding the clinical care of patients, epidemiological studies, and regulatory activity. Plaintiffs respond stating that Dr. Maggio does not intend to offer regulatory opinions. Instead, he opines that the EE and "Area Under the Curve"[23] (AUC) information in the labels for Yasmin/YAZ is misleadingly low (Doc. 2096 p. 14). Dr. Maggio has reviewed epidemiology data and does intend to offer testimony regarding the consistency between epidemiologic findings, the pharmacology, and the PK. Plaintiffs also state that Dr. Maggio does not opine regarding clinical practice or speculate about FDA practice. *Id*. at pp. 22-23.

3. Analysis

a. Qualifications

Dr. Maggio serves as the van Maanen Professor of Pharmacology and Experimental Therapeutics at the University Of Cincinnati College Of Medicine, where he is also a research scientist and where he chaired the Department of Pharmacology and Cell Biophysics for ten years (Doc. 2096 p. 12). He also acts as a visiting professor at the Harvard Medical School. *Id*. He earned a Ph.D. in

[23] The Area Under the Curve (or AUC) is the parameter that measures total exposure to a drug (and represents total drug delivered to the bloodstream). (Doc. 2096-1).

Organic Chemistry from Harvard University in 1981, and did post-doctoral work at Cambridge and Yale universities. *Id*.

Physicians engaged in the treatment of patients at the College of Medicine have contacted Dr. Maggio for his pharmacology opinions regarding safety, efficacy and adverse drug events. (Doc. 2096-2 pp. 409-410). As an expert in the pharmacology of prescription drugs, Dr. Maggio is familiar with the pharmacologic properties of COCs (Doc. 2096 p. 12). He has developed course material and instructed medical students concerning the pharmacology of drugs, including both pharmacodynamics and pharmacokinetic properties of prescription pharmaceuticals. *Id*.

b. Qualification Based Objections

Bayer does not object to Dr. Maggio's expertise as a pharmacologist. Considering the Dr. Maggio's professional background and education, the Court concludes that he is well qualified to offer an opinion regarding the pharmacology of Yasmin and YAZ and regarding whether that pharmacology increases a woman's risk of VTE.

Bayer does contend that Dr. Maggio is not qualified to offer testimony on a range of topics because such topics are outside Dr. Maggio's area of expertise. Specifically, Bayer contends that Dr. Maggio should not be permitted to testify regarding SHBG, APC^{res}, and epidemiology data.

First, as the Court has discussed in relation to other experts, the fact that Dr. Maggio is not a hematologist is not at all decisive. *See Doe v. Cutter*

Biological, Inc., 971 F.2d 375, 385 (9th Cir. 1992) ("Ordinarily, courts impose no requirement that an expert be a specialist in a given field, although there may be a requirement that he or she be of a certain profession, such as a doctor."). This is particularly evident in light of Dr. Maggio's pharmacology credentials and his experience as a researcher and instructor.

Considering these factors, clearly, Dr. Maggio is capable of understanding the data reported in studies evaluating SHBG and APC^{res}. The same is true with regard to epidemiological data. Moreover, after reviewing the available epidemiological, SHBG, and APC^{res} data, Dr. Maggio has formed opinions regarding whether the data in this literature is consistent with his proffered opinions. Summarizing or synthesizing data from different fields for the purpose of identifying consistencies and forming an opinion based on the totality of the evidence is perfectly appropriate. To the extent that Bayer disagrees with Dr. Maggio's view of the data he considered, they may explore those issues at trial during cross examination and via the presentation of contrary evidence and/or competing experts. Accordingly, Dr. Maggio may present testimony regarding the opinions outlined in sections D and E of plaintiffs' brief in response to Bayer's motion to exclude.

Bayer also contends that Dr. Maggio is not qualified to offer clinical or regulatory opinions. With regard to Dr. Maggio's alleged clinical opinions, plaintiffs state that Dr. Maggio does not opine regarding whether hypothetical physicians would have prescribed Bayer's products had different EE AUC values

been provided to them (Doc. 2096 p. 22). Plaintiffs state that Dr. Maggio does posit that prescribing physicians need to rely on EE AUC values contained in drug labels. This statement is not a clinical opinion and is not subject to exclusion under Rule 702. The Court also agrees that Dr. Maggio's opinion regarding whether new users should be started on Yasmin is not a clinical opinion. Rather, it is an admissible opinion based on Dr. Maggio's review of the relevant label, his pharmacological experience, and his EE exposure analysis.

With regard to objections about opinions relating to Bayer's labeling, the Court finds that Dr. Maggio is qualified to offer an opinion with regard to whether the information contained on the labeling is accurate or misleading. Dr. Maggio is an experienced pharmacologist; he does not need to be an FDA regulatory expert to form an opinion as to whether the pharmacology information in the Yasmin/YAZ labels is accurate or based on reliable data. As a pharmacologist, Dr. Maggio performed a thorough review of the studies, identified numerous issues, and described those issues in his report. Considering all of this, it is clear that Dr. Maggio is qualified to review the labels on Bayer's products and to form an opinion as to whether they are misleading.

c. Reliability

In addition to the qualifications already discussed, the following is pertinent to the reliability of all of Dr. Maggio's proffered opinions. In forming the statements currently at issue, Dr. Maggio consulted the following:

- Standard pharmacological methods and measurements (Doc. 2096 p. 13).

- Labeling information for various COCs, including YAZ and Yasmin. *Id*.

- Bayer's pharmacokinetic studies, as well as comparisons with Bayer's data to data from other published sources, such as product labels for other hormonal contraceptives. *Id* at pp. 13-14.
- Published scientific literature, all of which is cited in his report. *Id*. at p. 14.

As a general matter, the Court finds that Dr. Maggio's opinions are based on a reliable scientific methodology and a sufficient foundation.

d. Assistance to the Trier of Fact

The Court finds all of Dr. Maggio's opinions offer assistance to the trier of fact in its analysis of issues relevant to the dispute, as his testimony encompasses scientific opinions and observations not obvious to a lay-person.

e. Specific Objections

i. Dr. Maggio's EE Analysis and Opinions

Bayer contends that Dr. Maggio's opinions regarding the amount and variability of delivery of EE in YAZ and Yasmin should be excluded because they are based on a "made-for-litigation" theory and are not supported by scientific data or authority (Doc. 2025 pp. 2-10). The Court is not convinced by Bayer's arguments.

Further, as noted above, in reaching his EE related opinions, Dr. Maggio applied commonly accepted pharmacokinetic principles. He employed standard and reliable pharmacological techniques, methodology, and measurements. His conclusions are based on review of Bayer's pharmacokinetic studies, as well as comparisons with Bayer's data to data from other published sources, such as product labels for other hormonal contraceptives and published scientific

literature, all of which is cited in his report. Bayer has not established that Dr. Maggio's methodology was unsound. Instead, Bayer's arguments merely establish that Bayer disagrees with Dr. Maggio's EE related conclusions. Such disagreement does not warrant exclusion of Dr. Maggio's opinions on this matter.

Bayer's objections to Dr. Maggio's opinion regarding an unreasonably high exposure to EE due to variability are equally unconvincing. Dr. Maggio testified he is not opining that the mean AUC levels for YAZ or Yasmin are actually higher than for other COCs. Bayer contends this testimony establishes that Dr. Maggio's opinion is not supported by the data. The Court disagrees. Dr. Maggio's opinion relies on applying the high variability for Yasmin and YAZ to the mean concentrations of EE reflected in Bayer's studies. Considering the range of EE and the mean AUC level of EE shown in several of Bayer's studies, Dr. Maggio concluded that a large portion of women will be exposed to levels that exceed those banned by the FDA in 1988. The testimony cited by Bayer does not show that this opinion is unsupported by data. Moreover, to the extent that Bayer can identify data that is inconsistent with Dr. Maggio's opinion, such evidence should be explored during cross examination and is not grounds for exclusion.

Considering the above, the Court finds that Dr. Maggio's EE related opinions are reliable and are based on sound methodology and data. Thus, Dr. Maggio may offer testimony regarding his EE related opinions, including those opinions specifically described by the plaintiffs in section B of their response to Bayer's motion to exclude.

ii. Opinions as to Efficacy and Effectiveness

Plaintiffs state that Dr. Maggio does not opine that Bayer is less efficacious than other COCs. He does intend to offer opinions regarding whether the drugs provide an advantage in preventing conception and as to the effectiveness of YAZ for the additional approvals of acne and premenstrual dysphoric disorder. Dr. Maggio is qualified to review product labels, publications regarding efficacy, and other relevant efficacy data and form an opinion based thereon. The Court sees no grounds for excluding this testimony.

iii. Opinion Testimony Regarding FDA Actions

Bayer contends that Dr. Maggio speculates about "how the FDA evaluated YAZ and Yasmin pharmacokinetic data prior to approving those medicines, and about how the FDA evaluated epidemiological data reported after YAZ and Yasmin had been approved." (Doc. 2025 p. 16). Plaintiffs contend and the Court agrees that Bayer's argument mischaracterizes Dr. Maggio's proffered testimony. Plaintiffs state that Dr. Maggio intends to offer testimony criticizing the analysis performed by the FDA. Such opinion testimony is permissible. Dr. Maggio may also offer his observations and opinions of Bayer's calculations in which it defaults all data below the LLOQ of 25 down to zero, a practice that had previously been criticized by the FDA (Doc. 2096 p. 23). Plaintiffs contend that, in light of this criticism, it is not speculation for Dr. Maggio to opine that either the FDA now approves of the practice or FDA examiners were not aware of the

practice because the relevant information had been relegated to the appendices (Doc. 2096 p. 23). The Court agrees.

Dr. Maggio may also testify as to the importance of accurate PK data, based upon the recognized need to view all data in context. Bayer further contends that Dr. Maggio should not be permitted to testify as to whether EE serum levels and EE AUCs reported on the label created a false sense of comfort for medical officers responsible for the on-going review of product safety. Dr. Maggio, however, is not being offered to testify to the state of mind of FDA personnel.

iv. Purported Novelty of Science involving SHBG, APC^{res}, and EE

The Court has already reviewed the admissibility of testimony relating to or considering SHBG, APC^{res}, and EE data. For reasons already discussed, the Court finds that the relevant science and alleged associations involving these parameters is sufficiently sound and is not so novel as to warrant exclusion. Accordingly, to the extent that Bayer objects to Dr. Maggio's testimony in relation to these issues, their objections are overruled.

IV. CONCLUSION

For the foregoing reasons, the Court finds Dr. Rinder, Dr. Stier, Dr. Maggio and Dr. Rosing are qualified to opine as to the matters stated in their expert reports, as explained and clarified in plaintiffs' responses to Bayer's motions. Further, these opinions, as grounded in credible articles, studies, reports, internal Bayer documents, and personal experience are based on a reliable methodology. Accordingly, Bayer's arguments seeking exclusion of their opinions

are relevant to the weight and credibility of the proposed testimony. As such, Bayer's motions to exclude testimony of Dr. Rinder, Dr. Stier, Dr. Maggio and Dr. Rosing are **DENIED in their entirety** (Docs. 2030, 2028, 2025, and 2027).

SO ORDERED

David R. Herndon
2011.12.16
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Chief Judge
United States District Court **Date: December 16, 2011**